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(54) PELLETISED MEDICAMENT FORMULATIONS

(71) We, FISONS LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London, W.1., do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a pharmaceutical composition and its preparation.

In our British Patent No. 1,122,284 we have described and claimed an insufflator device for use in the administration of powdered medicaments by inhalation comprising a propeller-like device carrying a powder capsule rotatably mounted within a tubular housing by means of a shaft loosely journalled in a tapered bearing tube, the housing having a mouthpiece whereby a user can inhale air through the device. With that device, and other devices, e.g. that described in British Patent Specification No. 1,331,216, a user inhales air through the device which causes a powder container mounted therein to rotate. Powder within the container is fluidised and dispensed into the air stream which is inhaled by the user. For optimum dispensing it has been found that the powdered medicament particles should be comparatively free-flowing and yet should have an ultimate particle size of less than about ten microns to ensure adequate penetration of the medicament into the lungs of the user. These two requirements are *prima facie* mutually exclusive, since such fine powders are not sufficiently free-flowing. We have now found that this problem can be mitigated or overcome by forming the powdered medicament into small soft pellets which will fluidise satisfactorily within the container and yet which are of sufficiently low internal coherence to break up into finer particles of medicament of a therapeutically effective size in the turbulent airstream around the outside of the container. The formation of the medicament into soft pellets also aids the filling of the medicament into capsules and can enable diluents such as coarse lactose, which have in the past been incorporated into powder inhalation compositions, to be omitted from the composition.

Accordingly, the present invention provides a medicament in pellet form characterised in that the pellet is soft, is from 10 to 1000, preferably 30 to 500, microns in diameter and comprises an agglomeration of individual medicament particles, at least 90% and preferably at least 95% by weight of which have a diameter of less than 10 microns. The soft pellet preferably has an internal coherence such that the pellet remains intact when filled into a container, e.g. a capsule, using automatic filling machines, under conditions of transport and storage, and when fluidised within a container in the device from which it is intended to dispense the pellets and yet may be broken up into particles of a therapeutically effective size outside the container as it discharges from the container.

The medicament in the soft pellets of the invention may be selected from a wide range of powdered medicaments and may be in amorphous or crystalline form and may have been comminuted, e.g. ground, and, if necessary, classified or sieved, e.g. on an air jet sieve, to obtain a suitable size or may have been made by direct crystallisation to the desired size. However, it is preferred that the medicament be one which is to be administered by inhalation and which has a substantial number of particles, e.g. greater than 95% by weight, of less than 10 microns, e.g. from 0.01 to 10, and preferably from 1 to 4, microns diameter, before incorporation into the soft pellets of the invention. Desirably the individual medicament particles are self-agglomerative as is usually the case with a hygroscopic material. Examples of suitable medicaments include those suitable for the inhalation treatment of allergic airway diseases such as pharmaceutically acceptable salts of 1,3-bis(2-carboxychromon-5-yloxy)propan-2-ol,

pharmaceutically acceptable salts of 1,3-bis(2 - carboxychromon - 7 - yloxy)propan-2-ol, sympathomimetic amines (e.g. isoprenaline, ephedrine, or isoetharine and salts thereof), antibiotics (e.g. tetracycline), steroids, enzymes, vitamins and antihistamines. If desired a mixture of medicaments, e.g. a mixture of the disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)propan-2-ol (commonly known as disodium cromoglycate or cromolyn sodium) and isoprenaline, may be used.

The pellets may contain other ingredients, e.g. diluents colouring and flavouring agents. Where the medicament is not self agglomerative, e.g. hydroscopic, it may be desirable to incorporate a small portion of a binder into the soft pellets. Suitable binders include acacia gum, tragacanth gum, celluloses such as salts and ethers of carboxymethylcellulose, dextrans and sugar solutions. Where the medicament is not easily wetted it may be desirable to incorporate a small proportion of a surface active agent into, and/or to use a solvent in the preparation of, the soft pellets. In general we prefer not to use a binder, surface active agent or solvent in the soft pellets.

When the medicament is hygroscopic a small proportion of water, which, if necessary, is added to the medicament in the vapour phase is usually sufficient to act as binder. The moisture content of the material may be adjusted according to the physical properties of the particular material, for example, for disodium cromoglycate we prefer the soft pellets to contain less than 15%, and preferably from 8 to 11% by weight of water.

The size of the soft pellets of the invention may be varied within the range given above to suit the devices from which they are to be dispensed. For a given device there is an optimum pellet size for optimum fluidisation of the soft pellets and this may be readily determined by simple tests, e.g. by assessing the fluidisation of extremely strong pellets within the device which it is intended to use. We have also found that optimum dispensing of the soft pellets is related to the size of the hole in the container through which the pellets are to issue. We prefer that the pellets have a size of from one-twentieth to one-fifth of the diameter of the hole, which usually as a diameter of from 500 to 2000, e.g. about 700 to 1500 microns.

However, the internal coherence of the soft pellets may affect the desired size of the soft pellets since, as a generality, the larger the pellet the more internally coherent it must be in order to survive the forces experienced during fluidisation and it may be that the optimum pellet size (as determined by criteria other than internal coherence) would require that the pellet be so internally coherent for fluidisation that it is not broken up after it leaves the container. The optimum size of the soft pellet may therefore have to be reduced in order that a suitable internal coherence value may be used. However, as a general guide, we have found that satisfactory soft pellets for use in insufflators of the type described in British Patent No. 1,122,284 (commercially available under the Registered Trade Mark 'Spinhaler') and powered by human inhalation have a mean size in the range of from 50 to 250 microns, preferably a mean size in the range 120 to 160 microns and most preferably a mean size of about 140 microns.

As indicated above, the necessary internal coherence to be possessed by the soft pellet is a function of the conditions to be experienced both inside the container during fluidisation and outside the container for achieving break-up of the soft pellets. Large soft pellets must be of comparatively high internal coherence to withstand the forces generated during fluidisation in the container and yet must not be so strong that they do not break-up outside the container to form finer particles of a therapeutically effective size, which is preferably less than about 10 microns, e.g. from about 0.01 to 10, and preferably from 1 to 4, microns in diameter, for medicaments which are to penetrate deep into the lungs of a subject. The internal coherence of the soft pellet may therefore be varied over quite a wide range depending upon the energy available for breaking-up the soft pellet, and its size. The minimum internal coherence which may be possessed by the soft pellets will depend on their size and density, and on the forces to which the soft pellets are subject during fluidisation within the container. The internal coherence for a given case may be determined by simple test and modified as appropriate.

It will of course be appreciated that the method by which the soft pellets are to be filled into the container and under which the filled containers are transported and stored will also affect the minimum acceptable internal coherence in a given case, since appreciable break-up of the soft pellets should not occur under these conditions.

From the above, it will be appreciated that soft pellets having satisfactory properties may be obtained from a number of permutations of the size and coherence and optimum permutations within the above guide lines may be readily determined in each case by simple empirical tests. By way of an example, we

have found that for soft pellets which are to be dispensed from a gelatine capsule 6.4 mm in diameter and having two holes 0.8 mm in diameter in a shoulder thereof mounted in a device (commercially available under the Registered Trade Mark 'Spinhaler') according to British Patent No. 1,122,284 having a drawn wire shaft 2.03 mm diameter journalled in a hard nylon bearing tube 13 mm long and having an internal diameter of 2.08 mm at its inner end (i.e. that end housing the free end of the shaft) and of 2.44 mm at its other end, and wherein the capsule is rotated about its axis at a speed of about 1800 rpm by an air stream having a flow rate of 60 litres per minute it is desirable that the pellets have a mean size of about 140 microns. It is especially preferred that the pellets are made from disodium cromoglycate.

The soft pellets are preferably such that when put up in gelatine capsules 6.4 mm in diameter each containing 20 mg of the medicament as soft pellets they meet the criteria set out in the two tests below:—

(a) Dispersion test

The filled capsules are mounted in the capsule holder of the powder insufflator (having the specific dimensions set out immediately above) of British Patent Specification No. 1,122,284 and pierced to produce two holes of 0.8 mm diameter in a shoulder of the capsule. The dispersion of the medicament in the cloud delivered by the insufflator is determined using a modified version of the multistage liquid impinger described in British Patent Specification No. 1,081,881. The modifications incorporated in the present design are the addition of an extra impingement stage, and of a glass tube with a right angled bend approximately mid-way along its length. The extra impingement stage was added prior to the three stages described in British Patent Specification No. 1,081,881 and consists essentially of a jet of internal diameter 2.5 cm and a collection plate of diameter 5 cm designed to give an effective cut-off of approximately 12 microns at an air flow rate of 60 litres per minute. The glass tube, also of internal diameter 2.5 cm abutts the external end of the jet of the extra stage, and is coated internally with a film of polyethylene glycol 400 to provide a retentive surface for impinging particles. The insufflator is inserted into the upper, horizontal end of the glass tube and air drawn through at 60 litres per minute for 30 seconds. At least five capsules are treated in this manner and the results are averaged. The weight of the medicament collected on each stage of the impinger, on the glass tube, and on a filter paper positioned after the final stage is determined spectrophotometrically after solution in an appropriate volume of distilled water (or by any other appropriate method).

The soft pellets disperse satisfactorily if an average total for each capsule of at least 0.5 mg, preferably at least 1.0 mg and most preferably at least 1.5 mg of the medicament are found on a combination of the last two stages and filter paper of the multi-stage liquid impinger.

(b) Emptying test

The filled capsules are mounted in the capsule holder of the powder insufflator (having the specific dimensions set out above) of British Patent Specification No. 1,122,284 and pierced to produce two holes of 0.8 mm diameter in a shoulder of the capsule. The insufflator is placed in a device adapted to suck air through it for 2.5 seconds, the air flow rate at no time exceeding 60 litres per minute, and being held at 60 litres per minute for at least 2 seconds. The capsule mounted in the insufflator is subjected to 4 sucks as described and the weight of the material remaining in the capsule is determined. The above procedure is repeated 20 times and the average of the results determined.

The soft pellets empty satisfactorily if an average of at least 50%, preferably at least 75% and most preferably at least 90% by weight of the material has emptied from each capsule.

The following Strength test is also of relevance:—

The measure of the strength of the soft pellets of the invention may be achieved by means of a device (available from Instron Limited, Coronation Road, High Wycombe, Buckinghamshire, England as Model TM-SM) for the measurement of the stress/strain properties of materials. This device comprises a punch capable of fitting tightly into a die of 4 mms diameter and of 1.55 cms length. The die is open at the top end, save when the punch is inserted in that end, and is closed at the bottom end by a pressure sensitive plate. In operation the material to be tested is filled loosely into the die, the punch is moved at a constant speed into the die from the top end and the pressure on the pressure sensitive plate is recorded graphically. We have found that with soft pellets according to our invention a measurement of 10 g on the pressure sensitive plate occurs when the volume of the soft pellets has been reduced by about 25 to 35%, preferably about 30%, of the original volume of the soft pellets and that a measurement of 1 kg on the pressure sensitive plate occurs when the volume of the soft pellets has been reduced by about 50 to 70%, preferably about 60%, of the

original volume of the soft pellets. It is also noticeable that the measurement of the force on the pressure plate does not increase regularly, but in an approximately stepwise fashion. The increase in force on the pressure sensitive plate is not continuous, and decreases in the force with increasing penetration of the die may occur, as well as the expected increases in force with increasing penetration. It is believed that this irregular response to the applied pressure is due to the breakdown of the soft pellets.

From another aspect the invention also provides a capsule, cartridge or like container containing soft pellets of the invention, optionally in association with other pellets or particles. We prefer the container to be loosely filled to less than about 80% by volume, preferably less than about 50% by volume, with the soft pellets of the invention. The soft pellets should of course not be compacted into the container. We prefer the container, e.g. capsule, to contain from 10 to 100 mg of the soft pellets. The container may conveniently be pierced (and overcapped, e.g. with a plastic overcap) during its manufacture and then used, after removal of the overcap, in an inhalation device which has no piercing mechanism.

The soft pellets of the invention may be made by a number of methods.

Thus according to the invention there is provided a method for the manufacture of soft pellets according to the invention, which comprises subjecting particles of medicament which either are intrinsically, or have been rendered, self agglomerative to a controlled agglomeration. This controlled agglomeration may be carried out by,

(a) extruding the particles of medicament through an aperture,

(b) controlled agglomeration in a fluidised bed, or

(c) spray drying a solution or slurry of the medicament.

In method (a) which is the preferred method, finely divided medicament, e.g having a mean particle size in the range 0.01 to 10 microns may, if necessary, be subjected to an initial treatment to cause the powder particles to be self-agglomerative. Thus where the medicament is of a hygroscopic nature, the treatment may be carried out by wetting the powder particles by exposing them to a humid atmosphere, for example at a temperature of from about 15° to 50°C. Whilst the amount of water required to achieve adequate self-agglomerative properties may vary from medicament to medicament, it will not usually be necessary to increase the free water content of the powder beyond about 15% by weight, e.g. to from 5 to 10%. Where the medicament is non-hydroscopic, the necessary self-agglomerative properties may be imparted by the addition of a pharmaceutically acceptable binder, e.g. one selected from those mentioned earlier, or by treating the powder with a liquid (under carefully controlled conditions), which may be evaporated to produce bridges of a solid residue binding the powder particles, or which causes adequate interparticle contact. It will be appreciated that the nature of the binder may affect the coherence of the resultant pellet formed from treated medicament. A binder solution may, if desired, be used with a hygroscopic medicament in order to improve the internal coherence of the resultant pellet.

After the particles have been rendered self-agglomerative, they are passed through an aperture of approximately the size of the desired pellets, e.g. they are forced through the apertures of a vibrating sieve which is of similar mesh aperture to the desired final pellet size. The product of this passage through an aperture are shaped prepellets of the medicament.

In process (b) the fine particles of medicament to be formed into pellets may be suspended, together with any other ingredients it is desired to incorporate in the pellets, in a gas stream in a fluidised bed apparatus. When a hygroscopic material is to be formed into pellets the water content of the solid material may be adjusted by variation of the humidity of the gas stream passing through the fluidised bed. The medicament may be treated in the fluidised bed for a time and under conditions sufficient to produce pre-pellets of the desired internal coherence and size.

In process (c) a solution or more preferably a slurry, of the medicament may be spray-dried. We prefer to use a slurry of discrete medicament particles of the desired fine particle size, the slurry also containing any other ingredients it is desired to incorporate in the pellets. The liquid in the slurry is preferably a non-solvent or a poor solvent for the medicament so that no or not many medicament bridges are formed between the medicament particles during the spray drying. When a controlled amount of water is desired in the product a correspondingly greater amount of water may be included in the liquid in the slurry.

The extent of compaction of the treated powder during the controlled agglomeration will vary according to the method and powder used in the agglomeration. However, as a guide, we have found that suitable pre-pellets may be formed by process (a) from a powder of

disodium cromoglycate containing from about 8 to 10% by weight of water, by forcing the powder through a sieve having apertures of about 150 micron size.

The pre-pellets produced by any of the above processes may, if desired or necessary be subjected to tumbling and agitation using conventional methods until the desired size, shape and coherence of the pellets are achieved. We prefer a proportion, e.g. a majority, of the soft pellets, and especially soft pellets of disodium cromoglycate, to be approximately spherical. Conveniently the tumbling and agitation are carried out in a pan or drum type of pelletising machine. The treatment of the pre-pellets in such a machine is carried out until the majority of pellets in the charge have a size within the desired range. The size of the pre-pellets used and the conditions used in their agitation and tumbling may be varied in known manner to achieve the desired final size of soft pellet. The time for which the pellets are tumbled is, in certain circumstances, of importance to the production of viable soft pellets. The effect of the tumbling and agitation of the pellets is in general to strengthen them and increase their size slightly and to make them more nearly spherical in shape.

As indicated above the final product which issues from the agitation or tumbling step will have a range of sizes about the desired mean size. The product may be classified, e.g. sieved, to remove over and under sized material. The over and under sized material may be broken down into very fine particles and recycled to the agglomeration stage if desired.

The final soft pellets may be put up in any suitable form of container such as a capsule or cartridge. Where it is desired to use the pellets of the invention in association with other ingredients such as colourants, sweeteners or carriers such as lactose, these other ingredients may be applied to or admixed with the pellets using conventional techniques. We prefer the soft pellets of the invention to contain medicament and water only.

According to our invention we also provide a method of application of a medicament, e.g. disodium cromoglycate, to a patient by way of inhalation, the medicament being dispersed into an air stream, characterised in that a pierced capsule containing soft pellets according to the invention is rotated and vibrated in an air stream which is inhaled by the patient. The rotation and vibration may conveniently be produced by any one of a number of devices, e.g. the device of British Patent Specification No. 1,122,284. Disodium cromoglycate is known to be of use in the treatment of asthma and hay fever.

Shaped articles comprising sodium cromoglycate and less than 15% by weight of water, the article being other than a capsule containing sodium cromoglycate in admixture with lactose, are disclosed and claimed in our co-pending application No. 10074/77 (Serial No. 1,520,248).

The invention will now be illustrated by the following Example in which all parts and percentages are by weight unless otherwise stated.

Example

The moisture content of finely divided disodium cromoglycate having at least 98% thereof of particle size less than 10 microns and having a mass median diameter of from 1 to 3 microns was adjusted from an initial value of from 4 to 6% by weight to a value of about 9.5% by weight of exposure of the powder on a tray in an atmosphere of relative humidity 33% at 18 to 24°C.

After the desired moisture content had been achieved, the treated powder was tipped onto a 150 micron aperture stainless steel sieve screen mounted in a Russel vibratory sifter operating at a frequency of 1,000 cyles per second. The powder on the screen was forced through the sieve apertures using a stainless steel spatula pushed across the surface of the screen. The material issuing from the sifter as particles with a mean particle diameter of about 150 microns was fed directly to a drum pelletiser adapted to rotate about a horizontal axis. The drum of the pelletiser was approximately 0.3 m in internal diameter and 0.37 m long with one end closed and the other end provided with frusto conical shoulder leading to a 0.18 m orifice through which material could be charged to or removed from the drum. The interior of the drum was highly polished. Two kilograms of the material from the sifter were loaded into the drum which was then rotated at a peripheral speed of 0.38 m per second ±0.025 m per second for 15 minutes. At the end of this time the soft pellets had a mean particle diameter of 135 microns and not more than 10% by weight was retained on a 350 micron aperture sieve and not less than 90% by weight was retained on a 63 micron aperture sieve. The moisture content of the final soft pellets was in the range 8.5 to 10.5% by weight.

It will be appreciated that those steps of the process carried out after adjustment of the moisture content of the initial powder should be carried out under conditions of controlled humidity so as not to alter the water content of the powder appreciably.

The soft pellets produced by the above

procedure are approximately spherical, and have an open and loose structure and a fluffy surface when viewed under a microscope.

Up to 90 mg, e.g. 40 to 60 mg, of the above soft pellets were placed in a gelatine capsule having two holes 0.8 mm in diameter pierced in the shoulder thereof which was mounted in a device as described in British Patent No. 1,122,284 having the detailed construction and dimensions referred to above. When air at a flow rate of 60 litres per minute was passed through this device, it was found that the charge in the capsule was consistently completely dispensed into the airstream and broken up to provide a cloud of very fine particles suitable for inhalation.

By way of constrast, when the initial micronised powder from which the pellets had been prepared was tested under identical conditions, comparatively little of the powder was dispensed from the capsule and the amount dispensed varied inconsistently from test to test.

Similar results were obtained when 1,3-bis(2-carboxychromon-7-yloxy)propan-2-ol disodium salt (6% water), isoprenaline sulphate and tetracycline were subjected to the procedure of the Example to obtain soft pellets.

WHAT WE CLAIM IS:—

1. A medicament in pellet form characterised in that the pellet is soft, is from 10 to 1000 microns in diameter and comprises an agglomeration of individual medicament particles at least 90% of which have a diameter of less than 10 microns.

2. A medicament according to Claim 1, wherein the pellet is from 30 to 500 microns in diameter.

3. A medicament according to Claim 2, comprising a plurality of soft pellets of mean size of from 50 to 250 microns.

4. A medicament according to Claim 3, wherein the mean size is from 120 to 160 microns.

5. A medicament according to Claim 4, wherein the mean size is 140 microns.

6. A medicament according to any one of the preceding claims, wherein at least 95% by weight of the medicament particles have a diameter of less than 10 microns.

7. A medicament according to Claim 6, wherein at least 95% by weight of the medicament particles have a diameter of from 0.01 to 10 microns.

8. A medicament according to Claim 6, wherein at least 95% by weight of the medicament particles have a diameter of from 1 to 4 microns.

9. A medicament according to any one of the preceding claims, wherein the individual medicament particles are self-agglomerative.

10. A medicament according to any one of the preceding claims, wherein the medicament is hygroscopic.

11. A medicament according to any one of the preceding claims comprising an inhalation medicament for the treatment of allergic airway disease.

12. A medicament according to Claim 11, wherein the inhalation medicament comprises a pharmaceutically acceptable salt of 1,3-bis(2-carboxychromon-5-yloxy)propan-2-ol.

13. A medicament according to Claim 12, wherein the inhalation medicament comprises disodium cromoglycate.

14. A medicament according to Claim 13, wherein the inhalation medicament comprises disodium cromoglycate and isoprenaline.

15. A medicament according to any one of the preceding claims, comprising a diluent.

16. A medicament according to any one of the preceding claims, comprising a binder.

17. A medicament according to any one of the preceding claims, comprising a surface active agent.

18. A medicament according to Claim 13, comprising less than 15% by weight of water.

19. A medicament according to Claim 18, comprising from 8 to 11% by weight of water.

20. A medicament according to any one of the preceding claims, wherein in the Dispersion test as hereinbefore described, an average total of at least 0.5 mg of medicament is found on a combination of the last two stages and filter paper of the multi-stage liquid impinger.

21. A medicament according to Claim 20, wherein an average total of at least 1.0 mg of medicament is found on a combination of the last two stages and filter paper of the multi-stage liquid impinger.

22. A medicament according to Claim 21, wherein an average total of at least 1.5 mg of medicament is found on a combination of the last two stages of the multi-stage liquid impinger.

23. A medicament according to any one of preceding claims, wherein, in the Emptying test as hereinbefore described, an average of at least 50% by weight of the material has emptied from each capsule.

24. A medicament according to Claim 23, wherein an average of at least 75% by weight of the material has emptied from each capsule.

25. A medicament according to Claim 24, wherein an average of at least 90% by

weight of the material has emptied from each capsule.

26. A medicament according to any one of Claims 1 to 19, wherein the pellets are such that in the Strength test as hereinbefore described, a measurement of 10 g on the pressure sensitive plate occurs when the volume of the soft pellets has been reduced by 25 to 35%.

27. A medicament according to Claim 26, wherein a measurement of 10 g on the pressure sensitive plate occurs when the volume of the soft pellets has been reduced by 30%.

28. A medicament according to Claim 26, wherein a measurement of 1 kg on the pressure sensitive plate occurs when the volume of the soft pellets has been reduced by 50 to 70%.

29. A medicament according to Claim 28, wherein a measurement of 1 kg on the pressure sensitive plate occurs when the volume of the soft pellets has been reduced by 60%.

30. A medicament according to any one of Claims 1 to 19 or 26 to 29, wherein, in the Strength test as hereinbefore described, the increasing penetration of the die produces both increases and decreases in the force on the pressure sensitive plate.

31. A medicament according to any one of the preceding claims, wherein the soft pellet is spherical.

32. A medicament according to any one of the preceding claims, containing a colourant, sweetener or diluent.

33. A container containing a medicament according to any one of the preceding claims.

34. A container according to Claim 33 which is a capsule.

35. A container according to Claim 34 which is loosely filled to less than 80% by volume with the medicament in soft pellet form.

36. A container according to Claim 34 which is loosely filled to less than 50% by volume with the medicament in soft pellet form.

37. A container according to any one of Claims 33 to 36 containing from 10 to 100 mg of the medicament in soft pellet form.

38. A container according to any one of Claims 33 to 37 which is pierced.

39. A method for the manufacture of a medicament in pellet form, wherein the pellet is soft, is from 10 to 100 microns in diameter and comprises an agglomeration of individual medicament particles at least 90% of which have a diameter of less than 10 microns, which comprises controlled agglomeration of medicament comprising individual medicament particles at least 90% of which have a diameter of less than 10 microns.

40. A method according to Claim 39, wherein the controlled agglomeration comprises extruding the medicament comprising individual medicament particles through an aperture.

41. A method according to Claim 40, wherein the controlled agglomeration comprises forcing the medicament comprising individual medicament particles through a sieve of similar mesh size to the desired final pellet size.

42. A method according to any one of Claims 39 to 41, wherein the medicament comprising individual medicament particles is subjected to an initial treatment to cause the particles to be self-agglomerative.

43. A method according to Claim 42, wherein the medicament is hygroscopic and the initial treatment comprises wetting the powder particles by exposing them to a humid atmosphere.

44. A method according to Claim 43, wherein the particles are exposed to the humid atmosphere at a temperature of from 15 to 50°C.

45. A method according to any one of Claims 39 to 42, wherein the medicament is non-hygroscopic and self-agglomerative properties are imparted by the addition of a pharmaceutically acceptable binder.

46. A method according to Claim 39, wherein the controlled agglomeration is effected in a fluidised bed.

47. A method according to Claim 39, wherein the controlled agglomeration comprises spray drying a solution or slurry of the medicament.

48. A method according to any one of Claims 39 to 47, wherein the product of the controlled agglomeration is subjected to tumbling and agitation.

49. A method according to Claim 48, wherein the tumbling and agitation are carried out in a pan or drum type of a pelletising machine.

50. A method according to any one of Claims 39 to 49, wherein the product is classified to remove over and under sized material.

51. A method according to Claim 39 and substantially as hereinbefore described.

52. A method according to Claim 39 and substantially as hereinbefore described in the Example.

53. A medicament in soft pellet form

when made by a process according to any one of claims 39 to 52.

54. A method of dispersing a medicament into an air stream, wherein a pierced capsule containing a plurality of soft pellets according to any one of Claims 1 to 32 is rotated and vibrated in an air stream.

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